09/126,559

Set	Items	Description
S1	2384033	DRUG? ?
S2	45592	ANTIVIRAL? ?
S3	100722	SUSCEPTIBILITY
S4	1519592	RESISTANCE
S5	9768	HEPATITIS(W)C(W)VIRUS
S6	9688	HCV
S7	5591	ANTI(W)VIRAL? ?
S8	2	RESISTANCE(W)TEST(W)VECTOR
S9	306800	INDICATOR OR REPORTER
S10	1077419	EXPRESS?
S11	2405761	S1 OR S2 OR S7
S12	1587587	S3 OR S4
S13	13148	S5 OR S6
S14	346	INTERNAL(W)RIBOSOME(W)ENTRY(W)SITE
S15	676	IRES
S16	812	S14 OR S15
S17	191	S11(S)S12(S)S13
S18	302192	VECTOR? ? OR PLASMID? ? OR COSMID? ?
S19	136	S17 AND S18
S20	133	S19 AND S10
S21	38	S20 NOT PY>1997
S22	38	RD (unique items)
S23	66	S17 NOT PY>1997
S24	28	S23 NOT S22
S25	408224	S11/AB
S26	757126	S12/AB
S27	9385	S13/AB
S28	26463	S25 AND S26
S29	30	S28 AND S13
S30	15	S29 NOT PY>1997
S31	15	RD (unique items)
S32	165	AU="CAPON D" OR AU="CAPON D J" OR AU="CAPON DA" OR AU="CAPON DANIEL" OR AU="CAPON DANIEL J" OR AU="CAPON DANIEL JEFFREY" OR AU="CAPON DANIEL JEFFREY US" OR AU="CAPON DANIEL JEFFRY" OR AU="CAPON DJ"
S33	18	AU="WHITCOMB J M" OR AU="WHITCOMB JEANNETTE" OR AU="WHITCOMB JEANNETTE DR" OR AU="WHITCOMB JEANNETTE M" OR AU="WHITCOMB JM"
S34	21	AU="PARKIN N" OR AU="PARKIN N T" OR AU="PARKIN NEIL T" OR AU="PARKIN NT"
S35	200	S32 OR S33 OR S34
S36	138	S35 NOT PY>1997
S37	135	RD (unique items)
S38	360	S27 AND S18
S39	44	S38 AND S9
S40	21	S39 NOT PY>1997
S41	21	RD (unique items)
S42	6	PERMUTED(S)PROMOTOR
S43	5	S42 NOT PY>1997
S44	5	RD (unique items)
S45	348	S13 AND S11 AND S12
S46	157	S45 NOT S17
S47	74	S46 NOT PY>1997
S48	74	RD (unique items)

?

8/3/1 (Item 1 from file: 340)
DIALOG(R)File 340:CLAIMS(R)/US Patent

3072560 9839091
C/**COMPOSITIONS AND METHODS FOR DETERMINING ANTI-VIRAL DRUG SUSCEPTIBILITY AND RESISTANCE AND ANTI-VIRAL DRUG SCREENING; MEASUREMENT, CALIBRATION GENE EXPRESSION**
Inventors: Capon Daniel (US); Petropoulos Christos J (US)
Assignee: ViroLogic Inc Assignee Code: 47675

	Patent Number	Issue Date	Applic Number	Applic Date
Patent:	US 5837464	19981117	US 97790963	19970129
Priority Applic:			US 97790963	19970129
Provisional Applic:			US 60-10715	19960129

Calculated Expiration: 20170129

8/3/2 (Item 1 from file: 654)
DIALOG(R)File 654:US Pat.Full.

02874739
Utility
COMPOSITIONS AND METHODS FOR DETERMINING ANTI-VIRAL DRUG SUSCEPTIBILITY AND RESISTANCE AND ANTI-VIRAL DRUG SCREENING
[Measurement, calibration gene expression]

PATENT NO.: 5,837,464
ISSUED: November 17, 1998 (19981117)
INVENTOR(s): Capon, Daniel, Hillsborough, CA (California), US (United States of America)
Petropoulos, Christos J., Half Moon Bay, CA (California), US (United States of America)
ASSIGNEE(s): ViroLogic, Inc , (A U.S. Company or Corporation), S. San Francisco, CA (California), US (United States of America)
[Assignee Code(s): 47675]
APPL. NO.: 8-790,963
FILED: January 29, 1997 (19970129)
FULL TEXT: 6433 lines
?

22/3,AB/1 (Item 1 from file: 654)
DIALOG(R)File 654:US Pat.Full.

02724627

Utility
METHODS AND COMPOSITIONS FOR INHIBITING PRODUCTION OF REPLICATION COMPETENT VIRUS
[**Vector** directing **expression** of retroviral structural polypeptide comprising promoter, gene construct comprising nucleic acid molecule coding for polypeptide and biologically inactive inhibitory molecule, polyadenylation signal]

PATENT NO.: 5,698,446
ISSUED: December 16, 1997 (19971216)
INVENTOR(s): Klump, Wolfgang M., Del Mar, CA (California), US (United States of America)
Jolly, Douglas J., Leucadia, CA (California), US (United States of America)
ASSIGNEE(s): Chiron Corporation, (A U.S. Company or Corporation), US (United States of America)
[Assignee Code(s): 11661]
APPL. NO.: 8-305,699
FILED: September 07, 1994 (19940907)
FULL TEXT: 2013 lines

ABSTRACT

The present invention provides methods and compositions for inhibiting the production of replication competent virus. The invention comprises nucleic acid cassettes encoding a non-biologically active inhibitory molecule which are incorporated into packaging cells and recombinant **vector** constructs. Upon recombination between various **vector** construct contained within the producer cell, a biologically active molecule is produced which kills the cell, thereby inhibiting production of replication competent virus.

22/3,AB/6 (Item 6 from file: 654)
DIALOG(R)File 654:US Pat.Full.

02700749

Utility
RIBONUCLEASE RESISTANT VIRAL RNA STANDARDS
[Nucleic acid encapsulated by bacteriophage protein]

PATENT NO.: 5,677,124
ISSUED: October 14, 1997 (19971014)
INVENTOR(s): DuBois, Dwight B., Austin, TX (Texas), US (United States of America)
Winkler, Matthew M., Austin, TX (Texas), US (United States of America)
Pasloske, Brittan L., Austin, TX (Texas), US (United States of America)
ASSIGNEE(s): Ambion, Inc , (A U.S. Company or Corporation), Austin, TX (Texas), US (United States of America)
Cenetron Diagnostics LLC, (A U.S. Company or Corporation), Austin, TX (Texas), US (United States of America)
[Assignee Code(s): 32084; 43403]
APPL. NO.: 8-675,153
FILED: July 03, 1996 (19960703)
FULL TEXT: 1847 lines

ABSTRACT

The present invention is directed to the process of creating a recombinant nucleic acid standard which is resistant to ribonuclease digestion and is non-infectious. A single strand of recombinant nucleic acid is encapsidated by bacteriophage proteins. The recombinant nucleic acid is a hybrid sequence encoding bacteriophage proteins and a specific non-bacteriophage sequence. A non-bacteriophage RNA sequence can be used as an RNA standard to help quantify the number of RNA molecules in an unknown sample. The recombinant RNA in its packaged form is highly resistant to ribonucleases, insuring that the RNA standard is not compromised by inadvertent ribonuclease contamination. These "ARMORED RNA" standards are ideal as RNA standards for the quantification of RNA viruses such as HIV and HCV from human body fluids such as blood and cerebrospinal fluid.

22/3,AB/7 (Item 7 from file: 654)
DIALOG(R)File 654:US Pat.Full.

02693166

Utility
RECOMBINANT FOWLPOX VIRUS

PATENT NO.: 5,670,367
ISSUED: September 23, 1997 (19970923)
INVENTOR(s): Dorner, Friedrich, Vienna, AT (Austria)
Scheiflinger, Friedrich, Orth/Donau, AT (Austria)
Falkner, Falko Gunter, Mannsdorf, AT (Austria)
ASSIGNEE(s): Immuno Aktiengesellschaft, (A Non-U.S. Company or Corporation)
, Vienna, AT (Austria)
[Assignee Code(s): 53908]
APPL. NO.: 8-232,463
FILED: April 22, 1994 (19940422)
PRIORITY: 91114300, EP (European Patent Office), August 26, 1991
(19910826)

This application is a continuation of application Ser. No. 07-935,313, filed Aug. 26, 1992, abandoned.

FULL TEXT: 4665 lines

ABSTRACT

An improved method is described to prepare recombinant fowlpox virus for the **expression** of proteins or for use as a vaccine. The new method uses for the insertion of foreign DNA an intergenic region which is located between the FPV thymidine kinase (tk)gene and the 3'-open reading frame. Said intergenic region is enlarged to comprise one or more unique restriction sites, thereby allowing insertion of foreign DNA in such a way that the FPV tk-gene remains intact and codes for the entire thymidine kinase. New strong poxvirus promoters are presented and new FPV host virus strains carrying a vaccinia virus thymidine kinase gene and an E. coli lacZ gene as a novel non-essential site. The novel fowlpox virus host strains allow the use of any insertion **plasmid** carrying vaccinia virus tk-gene flanking regions.

22/3,AB/22 (Item 22 from file: 654)
DIALOG(R)File 654:US Pat.Full.

02612413

Utility
HEPATITIS B VIRUS MUTANTS, REAGENTS AND METHODS FOR DETECTION
[Diagnosis, vaccines]

PATENT NO.: 5,595,739
ISSUED: January 21, 1997 (19970121)
INVENTOR(s): Carman, William F., Glasgow, GB (United Kingdom)
Decker, Richard H., Deerfield, IL (Illinois), US (United States of America)
Wallace, Lesley, Glasgow, GB (United Kingdom)
Mimms, Larry T., Lake Villa, IL (Illinois), US (United States of America)
Solomon, Larry R., Mundelein, IL (Illinois), US (United States of America)
ASSIGNEE(s): Abbott Laboratories, (A U.S. Company or Corporation), Abbott Park, IL (Illinois), US (United States of America)
[Assignee Code(s): 152]
APPL. NO.: 8-59,031
FILED: May 07, 1993 (19930507)
FULL TEXT: 2059 lines

ABSTRACT

Mutant Hepatitis B Virus (HBV) nucleic acid sequences useful for a variety of diagnostic and therapeutic applications, kits for using the HBV nucleic acid sequences, HBV immunogenic particles, and a method for producing antibodies to HBV. Also provided are methods for producing antibodies, polyclonal or monoclonal, from the HBV nucleic acid sequences.
?

31/3,AB/1 (Item 1 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09690467 97449199
Therapy of hepatitis C: overview.
Lindsay KL
Department of Medicine, University of Southern California, Los Angeles 90033-4581, USA.
Hepatology (UNITED STATES) Sep 1997, 26 (3 Suppl 1) p71S-77S, ISSN 0270-9139 Journal Code: GBZ
Languages: ENGLISH
Document type: CONSENSUS DEVELOPMENT CONFERENCE; CONSENSUS DEVELOPMENT CONFERENCE, NIH; JOURNAL ARTICLE; REVIEW
Based on the first decade of research on alpha interferon in viral hepatitis, one can conclude that up to 40% of patients with compensated chronic hepatitis C and elevated alanine aminotransferase (ALT) levels will respond at least transiently to interferon. Four forms of alpha interferon have been evaluated in large numbers of patients with chronic hepatitis C: alfa-2b, alfa-2a, alfa-n1, and consensus interferon (CIFN). Responses are defined on the basis of biochemical (ALT) or virological (**hepatitis C virus** [**HCV**] RNA testing by polymerase chain reaction [PCR]) end points, and as end-of-treatment response (ETR) or sustained response (SR). Biochemical ETR rates to 6 months of therapy range from 35% to 50%, and SR rates 6 months after treatment from 8% to 21%. Although 6-month treatment courses are associated with a significant rate of relapse, 12 months of initial treatment and re-treatment regimens markedly improve the SR rate. Long-term follow-up evaluation in patients with an SR to interferon consistently show long-lasting and significant clinical, virological, and histological improvement. Finally, baseline factors that have been shown to be associated with SR to 6 months of treatment are not accurate enough to predict response. Therefore, the best treatment strategy is a therapeutic trial. Further studies of interferon therapy of hepatitis C are needed to define better virological end points useful in stopping therapy, to understand and better manage significant side effects of interferon, and to evaluate the histological effects of interferon in biochemical nonresponders. Also needed is a better understanding of the causes of **resistance** to interferon. Finally, newer therapeutic regimens such as the use of induction therapy and combination therapies with ribavirin, other **antiviral** agents, cytokines, and cytokine modifiers are of primary importance in eventually developing safe and effective means of treatment of hepatitis C.

31/3,AB/2 (Item 2 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09683658 97193758
Semiquantitative analysis of intrahepatic cytokine mRNAs in chronic hepatitis C.
Dumoulin FL; Bach A; Leifeld L; El-Bakri M; Fischer HP; Sauerbruch T; Spengler U
Department of General Internal Medicine and Institute of Pathology, University of Bonn, Germany.
J Infect Dis (UNITED STATES) Mar 1997, 175 (3) p681-5, ISSN 0022-1899 Journal Code: IH3
Languages: ENGLISH
Document type: JOURNAL ARTICLE
In order to characterize intrahepatic cytokine production, the mRNA levels of interleukin (IL)-2, -4, and -10 and interferon (IFN)-gamma were semiquantitatively determined by reverse-transcription competitive polymerase chain reaction in liver specimens from patients with chronic

hepatitis C (n = 23), chronic hepatitis B (n = 9), or primary biliary cirrhosis (n = 12) and normal liver (control) specimens (n = 12). IL-4 mRNA was undetectable. Similar IL-10 mRNA levels were detected in all samples studied, including the controls. Mean IFN-gamma and IL-2 mRNA levels were elevated in chronic inflammatory liver disease. IL-2 mRNA levels were similar in all 3 patient groups, but intrahepatic IFN-gamma mRNA levels were significantly higher in chronic hepatitis C than in chronic hepatitis B or primary biliary cirrhosis patients. This predominance of IFN-gamma may indicate a lower **susceptibility** of **hepatitis C virus** to the **antiviral** effects of this cytokine. The presence of IL-10 in normal liver may impair the induction of **antiviral** immune responses.

31/3,AB/9 (Item 9 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08603990 97201548
Analysis of hepatitis C virus **quasispecies populations by temperature gradient gel electrophoresis.**
Lu M; Funsch B; Wiese M; Roggendorf M
Institut fur Virologie, Universitatsklinikum Essen, Germany.
J Gen Virol (ENGLAND) Apr 1995, 76 (Pt 4) p881-7, ISSN 0022-1317
Journal Code: I9B
Languages: ENGLISH
Document type: JOURNAL ARTICLE
Hepatitis C virus (**HCV**) forms complex quasispecies populations which consist of a large number of closely related genetic variants. This genetic heterogeneity may cause antigenic variation or **drug resistance** . We used heteroduplex analysis by temperature gradient gel electrophoresis (TGGE) to characterize genetic variants of **HCV** . The high resolution of TGGE was proven by comparison of DNA sequence data of different cDNA clones from the **HCV** 5'NCR with their corresponding migration pattern in TGGE. Using this method we were able to identify virus variants of the **HCV** 5'NCR even if they only differed from each other by a single base. **HCV** populations from three patients with chronic hepatitis C were found to consist of genetic variants, although the degree of the heterogeneity varied. In addition, we compared the genetic heterogeneity of the core and E2 regions of the **HCV** genome in one patient. Our results demonstrate that TGGE is a useful tool for characterization of the genetic heterogeneity of virus populations in vivo.

31/3,AB/10 (Item 10 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08591853 96311182
Clinical relevance of hepatitis C virus **quasispecies.**
Enomoto N; Sato C
Second Department of Internal medicine, Faculty of Medicine, Tokyo Medical and Dental University, Japan.
J Viral Hepat (ENGLAND) 1995, 2 (6) p267-72, ISSN 1352-0504
Journal Code: CG0
Languages: ENGLISH
Document type: JOURNAL ARTICLE; REVIEW; REVIEW, TUTORIAL
It has been shown that **hepatitis C virus** (**HCV**) populations in infected individuals are composed of quasispecies with diverse mutations. The analysis of these variants may reveal mechanisms of the persistence of **HCV** infection, carcinogenesis and **resistance** to **antiviral** therapy. Recently, genetic features of interferon-resistant **HCV** have been elucidated through the analysis of interferon-resistant quasispecies, making it possible to predict interferon efficacy by detecting interferon-resistant strains.

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41/3,AB/1 (Item 1 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09296938 98007644
Efficient gene transfer into various mammalian cells, including non-hepatic cells, by baculovirus vectors.
Shoji I; Aizaki H; Tani H; Ishii K; Chiba T; Saito I; Miyamura T; Matsuura Y
Department of Virology II, National Institute of Infectious Diseases, Tokyo, Japan.
J Gen Virol (ENGLAND) Oct 1997, 78 (Pt 10) p2657-64, ISSN 0022-1317 Journal Code: I9B
Languages: ENGLISH
Document type: JOURNAL ARTICLE
A baculovirus (Autographa californica nucleopolyhedrovirus) **vector** containing a strong promoter, the CAG promoter, was developed to introduce foreign genes into mammalian cells. Recombinant baculoviruses carrying a **reporter** gene under the control of the CAG promoter were inoculated into various mammalian cell lines. High-level expression was observed not only in hepatocytes but also in other non-hepatic cell lines tested. Expression of the **reporter** gene was detected even 14 days after infection. The infectious titre of the recovered baculoviruses decreased significantly after infection, indicating that the baculoviruses did not replicate in mammalian cells. We then compared the efficiencies of gene expression by the baculovirus **vector** with that of a replication-defective adenovirus **vector** by using the same expression unit. The same level of expression was observed in HepG2, HeLa and COS7 cells by both **vectors** . Efficient expression and proper processing were observed in mammalian cells infected with baculoviruses carrying genes coding for structural regions of **hepatitis C virus** . These results suggest that the baculovirus **vector** is a good tool for gene delivery into various mammalian cells in order to study the function of foreign genes.

41/3,AB/2 (Item 2 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09276812 97415421
In vivo translational efficiency of different hepatitis C virus 5'-UTRs.
Buratti E; Gerotto M; Pontisso P; Alberti A; Tisminetzky SG; Baralle FE
International Centre for Genetic Engineering and Biotechnology, Trieste, Italy.
FEBS Lett (NETHERLANDS) Jul 14 1997, 411 (2-3) p275-80, ISSN 0014-5793 Journal Code: EUH
Languages: ENGLISH
Document type: JOURNAL ARTICLE
Initiation of translation in **hepatitis C virus** (**HCV**) is dependent on the presence of an internal ribosome entry site (IRES) contained in its 341-nt-long 5'-untranslated region (UTR). This region is very conserved among different isolates and has been used to classify **HCV** isolates in six different genotypes. These genotypes differ in nucleotide sequence that generally preserve the IRES structure. However, the small differences seen may be biologically and clinically significant as the **HCV** strains seem to differ from each other in several important ways, such as the behaviour of the viral infection and the response to interferon therapy. Therefore, differences in translational initiation efficiency amongst the various genotypes could provide an explanation for these phenomena. Using a bicistronic expression system we have compared the in vivo translational ability of the three most common European genotypes of **HCV** (1, 2, and 3). The results show that genotype 3 is less able than 1 and 2 to promote translation initiation. In addition, by site-directed mutagenesis of the sequence of the IRES domain III apical stem loop structure, we have shown

that the conservation of the primary nucleotide sequence and not only the structure, is important for the conservation of IRES function.

41/3,AB/7 (Item 7 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08260672 95133223
Pestivirus translation initiation occurs by internal ribosome entry.
Poole TL; Wang C; Popp RA; Potgieter LN; Siddiqui A; Collett MS
Oak Ridge National Laboratory, Biology Division, Tennessee 37831.
Virology (UNITED STATES) Jan 10 1995, 206 (1) p750-4, ISSN 0042-6822
Journal Code: XEA
Contract/Grant No.: HL43375, HL, NHLBI
Languages: ENGLISH
Document type: JOURNAL ARTICLE

The role of the 385 nucleotide 5' noncoding region (NCR) in the translation of the pestivirus genome was investigated. In vitro translation of an RNA transcript containing the 5' NCR of the bovine viral diarrhea virus (BVDV) genome followed by the coding sequence of the first gene product (p20) of the BVDV large open reading frame resulted in the synthesis of a 20-kDa polypeptide. Results from hybrid-arrest translation studies identified a region involving a predicted RNA stem-loop structure spanning nucleotides 154-261 within the 5' NCR that was important for p20 synthesis. An additional inhibitory oligonucleotide was complementary to the sequence at the base of this stem-loop and encompassed the initiating AUG at nucleotide 386. Antisense oligonucleotides both upstream and downstream of those that were inhibitory had no effect on p20 translation. RNA from a dicistronic expression **vector** in which the BVDV 5' NCR was inserted between two **reporter** genes, CAT and LUC, showed strong expression of the second (LUC) cistron upon in vitro translation. This expression was dramatically reduced in an analogous construct in which nucleotides 173-236 of the 5' NCR were deleted. Similar results were obtained when RNA from these same **vectors** was evaluated for expression after transfection into BHK cells. These results suggest that the BVDV 5' NCR contains an internal ribosome entry site for translation initiation. This translational mechanism is similar to that shown for **hepatitis C virus**, further demonstrating the close relationship between viruses of these two genera within the family Flaviviridae.

41/3,AB/12 (Item 2 from file: 654)
DIALOG(R)File 654:US Pat.Full.

02690507
Utility
MAMMALIAN EXPRESSION SYSTEMS FOR HCV PROTEINS

PATENT NO.: 5,667,992
ISSUED: September 16, 1997 (19970916)
INVENTOR(s): Casey, James M., Zion, IL (Illinois), US (United States of America)
Bode, Suzanne L., Zion, IL (Illinois), US (United States of America)
Zeck, Billy J., Gurnee, IL (Illinois), US (United States of America)
Yamaguchi, Julie, Chicago, IL (Illinois), US (United States of America)
Frail, Donald E., Libertyville, IL (Illinois), US (United States of America)
Desai, Suresh M., Libertyville, IL (Illinois), US (United States of America)

Devare, Sushil G., Northbrook, IL (Illinois), US (United States of America)
ASSIGNEE(s): Abbott Laboratories, (A U.S. Company or Corporation), Abbott Park, IL (Illinois), US (United States of America) [Assignee Code(s): 152]
APPL. NO.: 8-453,552
FILED: May 30, 1995 (19950530)

This is a division of U.S. patent application Ser. No. 08-417,478 filed Apr. 5, 1995 now abandoned, which is a continuation of 08-144,099 filed Oct. 28, 1993 now abandoned, which is a continuation of 07-830,024 filed Jan. 31, 1992, now abandoned.

FULL TEXT: 7353 lines

ABSTRACT

Mammalian expression systems for the production of **HCV** proteins. Such expression systems provide high yields of **HCV** proteins, and enable the development of diagnostic and therapeutic reagents which contain glycosylated structural antigens and also allow for the isolation of the **HCV** etiological agent.

41/3,AB/13 (Item 3 from file: 654)
DIALOG(R)File 654:US Pat.Full.

02627460
Utility
MAMMALIAN EXPRESSION SYSTEMS FOR HEPATITIS C VIRUS ENVELOPE GENES

PATENT NO.: 5,610,009
ISSUED: March 11, 1997 (19970311)
INVENTOR(s): Watanabe, Shinichi, Northbrook, IL (Illinois), US (United States of America)
Yamaguchi, Julie, Chicago, IL (Illinois), US (United States of America)
Desai, Suresh M., Libertyville, IL (Illinois), US (United States of America)
Devare, Sushil G., Northbrook, IL (Illinois), US (United States of America)
ASSIGNEE(s): Abbott Laboratories, (A U.S. Company or Corporation), Abbott Park, IL (Illinois), US (United States of America) [Assignee Code(s): 152]
APPL. NO.: 8-188,281
FILED: January 28, 1994 (19940128)

FULL TEXT: 2816 lines

ABSTRACT

Mammalian expression systems for the production of **HCV** E1-E2 fusion proteins. Such expression systems provide high yields of **HCV** proteins extracelluarly, and enable the development of diagnostic, vaccine and therapeutic reagents which contain glycosylated structural antigens and also allow for the isolation of the **HCV** etiological agent.
?

48/3,AB/1 (Item 1 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09644116 98340243
Synthetic antisense oligodeoxynucleotides as potential drugs **against hepatitis C.**
Caselmann WH; Eisenhardt S; Alt M
Department of General Internal Medicine, Rheinische Friedrich-Wilhelms-Universitat, Bonn, Germany. Caselmann@Uni-Bonn.de
Intervirology (SWITZERLAND) 1997, 40 (5-6) p394-9, ISSN 0300-5526
Journal Code: GW7
Languages: ENGLISH
Document type: JOURNAL ARTICLE; REVIEW; REVIEW, TUTORIAL
Antisense oligodeoxynucleotides (ODNS) can be used to specifically inhibit hepatitis C viral gene expression. Due to its high degree of conservation and its important function as internal ribosomal entry site, the 5'-non-coding region of the **hepatitis C virus** has been the most effective target to inhibit translation so far. Inhibition of luciferase reporter gene expression of up to 96 +/- 2% has been achieved. Modifications of ODNs like phosphorothioate, methylphosphonate or benzylphosphonate modification of terminal or intramolecular internucleotide phosphates lead to altered lipophilicity and binding stability to its RNA target and **resistance** against serum nucleases. The mode of action of ODNs is mainly dependent on an efficient induction of RNase H activity. The uptake of ODNs occurs via receptor-mediated or absorptive and fluid-phase endocytosis. After release from the endosomes, ODNs may exert their effects by interaction with cytosolic or nuclear structures. Side effects can occur when this interaction affects intra- or extracellular targets essential for biological cell function. If these problems can be solved, antisense technology has the potential for future therapy of human disease.

48/3,AB/3 (Item 3 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09310408 98010017
Different susceptibilities of genetic variants of hepatitis C virus **(HCV) to interferon (IFN).**
Lu M; Wiese M; Funsch B; Roggendorf M
Institut fur Virologie, Universitatsklinikum Essen, Federal Republic of Germany.
Arch Virol (AUSTRIA) 1997, 142 (3) p581-8, ISSN 0304-8608
Journal Code: 8L7
Languages: ENGLISH
Document type: JOURNAL ARTICLE
Genetic variants of **HCV** may have different degrees of **resistance** to IFN and may therefore influence the outcome of IFN therapy. However, selection of **HCV** variants by IFN has not been investigated in detail. In this paper, heteroduplex analysis was used to monitor major changes of **HCV** populations in 4 chronically infected patients under IFN therapy. We found that a major variant of the **HCV** 5' non-coding region (5' NCR) emerged in a responder. In other patients although no new variant of the 5' NCR was identified, significant changes occurred within the core and E1 region of the **HCV** genome. Disappearance and emergence of **HCV** variants may reflect their different susceptibilities to IFN. Our results indicate that responses of **HCV** populations to IFN are complex and need to be characterized by analysis of multiple **HCV** genome regions.

48/3,AB/5 (Item 5 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

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09296947 97475410

Mutations in the NS5A gene of hepatitis C virus **in North American patients infected with** HCV **genotype 1a or 1b.**

Hofgartner WT; Polyak SJ; Sullivan DG; Carithers RL Jr; Gretch DR

Department of Laboratory Medicine, University of Washington Medical Center, Seattle, USA.

J Med Virol (UNITED STATES) Oct 1997, 53 (2) p118-26, ISSN 0146-6615 Journal Code: I9N

Contract/Grant No.: R29 AI39049-02, AI, NIAID; AI/DK 41320-02, AI, NIAID

Languages: ENGLISH

Document type: JOURNAL ARTICLE

Previous studies from Japan have described an association between a conserved sequence within the **hepatitis C virus** (**HCV**) genome and **resistance** to interferon (IFN) therapy for patients infected with **HCV** genotype 1b [Enomoto et al. (1995): Journal of Clinical Investigation 96: 224-230; Enomoto et al. (1996): New England Journal of Medicine 334:77-81]. The present study examines amino acid sequences surrounding the putative Interferon Sensitivity Determining Region (ISDR) of the NS5A gene of **HCV** in 21 North American patients with genotype 1a or 1b infection receiving recombinant IFN therapy. The ISDR consensus or intermediate pattern was observed in 13 of 14 NS5A clones from North American patients infected with genotype 1b. However, we found no evidence of the consensus ISDR sequence in any NS5A clones isolated from 15 patients with genotype 1a infection. In select cases, gel shift analysis showed no significant changes in the clonal frequency of the putative ISDR domain of **HCV** genotype 1a or 1b infected patients who were either nonresponsive to IFN therapy, or relapsed following withdrawal of IFN therapy. These results suggest that a conserved ISDR domain is neither associated with, nor responsible for, IFN **resistance** in North American patients infected with **HCV** genotype 1a, and demonstrate a need for further investigation into the reported association between ISDR consensus sequences and IFN **resistance** in genotype 1b clones.

48/3,AB/8 (Item 8 from file: 155)

DIALOG(R)File 155:MEDLINE(R)

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09260019 97201443

Pretreatment virus load and multiple amino acid substitutions in the interferon sensitivity-determining region predict the outcome of interferon treatment in patients with chronic genotype 1b hepatitis C virus **infection [see comments]**

Chayama K; Tsubota A; Kobayashi M; Okamoto K; Hashimoto M; Miyano Y; Koike H; Kobayashi M; Koida I; Arase Y; Saitoh S; Suzuki Y; Murashima N; Ikeda K; Kumada H

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Hepatology (UNITED STATES) Mar 1997, 25 (3) p745-9, ISSN 0270-9139 Journal Code: GBZ

Comment in Hepatology 1997 Mar;25(3):769-71

Languages: ENGLISH

Document type: JOURNAL ARTICLE

Hepatitis C virus (**HCV**) genotype 1b and high pretreatment virus load are predictive factors of poor response to interferon therapy in patients with chronic hepatitis C. To further examine the factors predicting the response to interferon in patients with genotype 1b infection, we analyzed 110 consecutive patients with **HCV** who were treated with a total of 624 million units of lymphoblastoid interferon alfa. Thirty-six patients (33%) were responders, while the remaining 74 patients (67%) were nonresponders. Multivariate analysis showed that a high virus titer (assessed by serum core protein level, P = .0021) and the presence of

more than two amino acid substitutions in the interferon sensitivity-determining region (ISDR) (P = .0036) correlated significantly with the response to interferon therapy. Because mutations analyzed by direct sequencing of polymerase chain reaction (PCR) products may reflect artifacts of direct sequencing, we further analyzed quasispecies of **HCV** in this region by cloning and sequencing. Although PCR-based analysis of responders with multiple amino acid substitutions in the ISDR showed the presence of a small amount of wild-type strain in their serum, the results obtained by direct sequencing and cloning were essentially the same. A longitudinal study of quasispecies in 2 patients who showed a dramatic change in the virus titer showed no conversion from wild type to mutant or vice versa. Our results indicate that amino acid substitutions and virus load are independent predictors of the response to interferon therapy. The ability of some patients with no mutation in the ISDR or high virus load to eliminate the virus suggests the presence of other unidentified factors, host or viral, that influence the response to interferon therapy.

48/3,AB/9 (Item 9 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09260018 97201442
Mutations in the nonstructural 5A gene of European hepatitis C virus **isolates and response to interferon alfa [see comments]**
Zeuzem S; Lee JH; Roth WK
Medizinische Klinik II, Klinikum der Johann Wolfgang Goethe-Universitat, Frankfurt a.M., Germany.
Hepatology (UNITED STATES) Mar 1997, 25 (3) p740-4, ISSN 0270-9139
Journal Code: GBZ
Comment in Hepatology 1997 Mar;25(3):769-71
Languages: ENGLISH
Document type: JOURNAL ARTICLE
The response rate to interferon alfa (IFN-alpha) in patients infected with **hepatitis C virus** (**HCV**) genotype 1 isolates is poor. A region associated with sensitivity to IFN has been identified in subtype **HCV** -1b isolates from Japanese patients in the carboxyterminal half of the nonstructural protein NS5A (between codon 2209 and 2248). **HCV** -1b isolates with at least four amino acid changes in this region compared with the **HCV** -1b prototype sequence were sensitive, whereas isolates identical to the prototype sequence were resistant to IFN-alpha. Patients infected with **HCV** -1b isolates carrying 1 to 3 mutations in NS5A(2209-2248) showed an intermediate response pattern. Because of the large geographical differences observed for **HCV** it is unknown whether this putative IFN-alpha sensitivity determining region is also predictive for European isolates. We analyzed 32 patients chronically infected with **HCV** -1a or **HCV** -1b isolates who were treated with 3 million units of recombinant IFN-alpha three times per week for 1 year. Before initiation, during, and after treatment serum **HCV** -RNA levels were assessed by a quantitative reverse-transcription polymerase chain reaction (RT-PCR) assay. The amino acid sequence of NS5A(2209-2248)was determined by direct sequencing of the PCR-amplified **HCV** genome and was compared with the reference sequence **HCV** -J. In patients chronically infected with subtype **HCV** -1a or **HCV** -1b the initial or sustained response to IFN-alpha was not related to the number of amino acid substitutions in the NS5A(2209-2248) region. In addition, the number of amino acid changes in NS5A(2209-2248) was not related to pretreatment **HCV** -RNA serum levels. In three patients with a pronounced initial decline of **HCV** -RNA levels (>3 log) sequence analyses of NS5A(2209-2248) were performed before and after therapy. Compared with the pretreatment amino acid sequence the **HCV** isolates of these patients revealed more mutations in the NS5A(2209-2248) region after therapy. These findings from European patients indicate that the NS5A(2209-2248) region of **HCV** does not represent a common interferon sensitivity determining region.

48/3,AB/19 (Item 19 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08589239 96155132
Hepatitis C virus **quasispecies populations during chronic hepatitis C infection.**
Enomoto N; Sato C
Second Dept of Internal Medicine, Faculty of Medicine, Tokyo Medical and Dental University, Japan.
Trends Microbiol (ENGLAND) Nov 1995, 3 (11) p445-7, ISSN 0966-842X Journal Code: B1N
Languages: ENGLISH
Document type: JOURNAL ARTICLE; REVIEW; REVIEW, TUTORIAL
Hepatitis C virus populations in infected individuals consist of quasispecies with diverse mutations. These quasispecies have different biological properties, and the analysis of these variants has led to new interpretations of viral persistence, carcinogenesis and **resistance** to interferon therapy.

48/3,AB/20 (Item 20 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08587326 96091314
Predictors of sustained response, relapse and no response in patients with chronic hepatitis C treated with interferon-alpha.
Chemello L; Cavalletto L; Noventa F; Bonetti P; Casarin C; Bernardinello E; Pontisso P; Donada C; Casarin P; Belussi F; et al
Clinica Medica 2, University of Padova, PD, Italy.
J Viral Hepat (ENGLAND) 1995, 2 (2) p91-6, ISSN 1352-0504 Journal Code: CG0
Languages: ENGLISH
Document type: CLINICAL TRIAL; JOURNAL ARTICLE; RANDOMIZED CONTROLLED TRIAL
Three main patterns of response are seen when interferon-alpha (IFN-alpha) is used for the treatment of chronic hepatitis C: 1 sustained response with alanine-aminotransferase (ALT) normalization that is maintained after cessation of therapy, with or without clearance of serum **hepatitis C virus** (**HCV**) RNA; 2 transient response with ALT normalization during therapy followed by relapse after its withdrawal, and 3 no response with no or only partial reduction in ALT levels. In order to define variables that could predict each of these three types of response we studied 321 cases of chronic hepatitis C treated with IFN-alpha in two consecutive trials conducted in our Unit. By univariate analysis, age < 45 years ($P < 0.01$), known disease duration < 60 months ($P < 0.01$), normal gamma-glutamyl-transpeptidase (gamma GT) levels ($P < 0.01$) and infection by **HCV** genotype 2 or **HCV** genotype 3 ($P < 0.01$) were found to be statistically associated with sustained response while age > 45 years ($P < 0.01$), body weight ($P = 0.05$), cirrhosis ($P < 0.01$) and elevated gamma GT levels ($P < 0.01$) were associated with no response. By multivariate analysis sustained response was predicted by **HCV** genotype 2 ($P < 0.01$) and **HCV** genotype 3 ($P < 0.01$), known disease duration ($P < 0.01$), patient's age ($P < 0.05$) and associated with the use of a more aggressive treatment schedule ($P < 0.05$). Transient response with relapse was predicted by known duration of disease ($P < 0.05$), **HCV** genotype 1 ($P < 0.05$) and female sex ($P < 0.05$). No response was statistically associated with elevated gamma GT levels ($P < 0.01$), higher body weight ($P < 0.05$) and with the less aggressive regimen of 3 MU of natural IFN-alpha given three times weekly for 6 months ($P < 0.05$). These results indicate that the **HCV** genotype as well as the schedule of treatment greatly affect the pattern of

response to IFN in chronic hepatitis C and allow us to define criteria to predict which type of response is more likely in individual patients.

48/3,AB/23 (Item 23 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08580799 95340824
Comparison of full-length sequences of interferon-sensitive and resistant hepatitis C virus **1b. Sensitivity to interferon is conferred by amino acid substitutions in the NS5A region.**
Enomoto N; Sakuma I; Asahina Y; Kurosaki M; Murakami T; Yamamoto C; Izumi N; Marumo F; Sato C
Second Department of Internal Medicine, Faculty of Medicine, Tokyo Medical and Dental University, Japan.
J Clin Invest (UNITED STATES) Jul 1995, 96 (1) p224-30, ISSN 0021-9738 Journal Code: HS7
Languages: ENGLISH
Document type: JOURNAL ARTICLE
We have previously demonstrated that sensitivity to interferon is different among **hepatitis C virus** (**HCV**) quasispecies simultaneously detected in same individuals and that interferon-resistant **HCV** quasispecies are selected during the treatment. To determine the genetic basis of their **resistance** to interferon, **HCV** genotype-1b was obtained from serum of three patients before and during interferon therapy, and their full-length nucleotide and deduced amino acid sequences were determined. Comparison of the pairs of interferon-resistant and interferon-sensitive **HCV** isolates in respective individuals demonstrated clusters of amino acid differences in the COOH-terminal half of the NS5A region (codon 2154-2383), which contained a common unique amino acid difference at codon 2218. Additional sequence data of the COOH-terminal half of the NS5A region obtained from six interferon-resistant and nine interferon-sensitive **HCV** confirmed the exclusive existence of missense mutations in a 40 amino acid stretch of the NS5A region around codon 2218 (from codon 2209 to 2248) in interferon-sensitive **HCV** . On the other hand, this region of interferon-resistant **HCV** was identical to that of prototype **HCV** genotype-1b (**HCV** -J, **HCV** -JTa, or HC-J4). We designated this region as the interferon sensitivity determining region. Thus, **HCV** genotype-1b with the prototype interferon sensitivity determining region appears to be interferon-resistant strains. The specific nature of these mutations might make it possible to predict prognostic effects of interferon treatment.

48/3,AB/31 (Item 31 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

07693335 94069717
Increased susceptibility **for CsA-induced hepatotoxicity in kidney graft recipients with chronic viral hepatitis C.**
Horina JH; Wirnsberger GH; Kenner L; Holzer H; Krejs GJ
Department of Medicine, Karl Franzens University, Graz, Austria.
Transplantation (UNITED STATES) Nov 1993, 56 (5) p1091-4, ISSN 0041-1337 Journal Code: WEJ
Languages: ENGLISH
Document type: JOURNAL ARTICLE
CsA-induced hepatotoxicity is a rare disorder in renal transplant recipients when low doses are administered and whole blood trough levels of CsA are regularly monitored. However, there is controversy about the clinical value of measuring CsA-metabolites, whose contribution to immunosuppression and toxicity is not fully understood. To assess the relation between low-dose CsA therapy and hepatotoxicity, we studied 128

renal transplant recipients attending our nephrology clinic. Eight of these patients had markedly elevated liver function tests. Three patients while receiving very low doses of oral CsA (< 3.8 mg/kg of body weight) presented marked derangements of CsA metabolism with abnormally increased CsA-metabolite levels. Parent **drug** levels were in the normal range. All 3 patients had chronic infection with **hepatitis C virus** and revealed histomorphologic evidence of hepatotoxicity. Hepatic dysfunction normalized when CsA was withdrawn or reduced by 50%. It is likely that **hepatitis C virus** infection interferes with CsA metabolism and/or biliary CsA-excretion and thus is responsible for CsA and/or metabolite-induced hepatotoxicity despite very low doses of CsA.

48/3,AB/40 (Item 6 from file: 348)
DIALOG(R)File 348:European Patents

00765862
ORDER fax of complete patent from Dialog SourceOne. See HELP ORDER 348
Methods and compositions for controlling translation of HCV **proteins**
Verfahren und Zusammensetzungen zur Kontrolle der Uberstetzung von HCV **-Proteine**
Procedes et compositions pour le controle de la traduction des proteines de HCV
PATENT ASSIGNEE:
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PATENT (CC, No, Kind, Date): EP 718400 A2 960626 (Basic)
EP 718400 A3 960703
APPLICATION (CC, No, Date): EP 95118443 930928;
PRIORITY (CC, No, Date): US 952799 920928
DESIGNATED STATES: AT; BE; CH; DE; DK; ES; FR; GB; GR; IE; IT; LI; LU; MC; NL; PT; SE
RELATED PARENT NUMBER(S) - PN (AN):
EP 662128 (EP 939224143)
INTERNATIONAL PATENT CLASS: C12N-015/11; C12N-015/51; C12N-015/67; C12N-015/86; A61K-031/70; A61K-047/48; A61K-048/00

ABSTRACT EP 718400 A3
Embodiments of the present invention feature methods and compositions for controlling the translation of viral peptides and proteins from viral nucleic acid, with particular applications to pestivirus and **HCV**. The methods and compositions feature control elements of the 5'UT region of the viral genome.
ABSTRACT WORD COUNT: 54

LANGUAGE (Publication,Procedural,Application): English; English; English
FULLTEXT AVAILABILITY:

Available Text	Language	Update	Word Count
CLAIMS A	(English)	EPAB96	336
SPEC A	(English)	EPAB96	8437

Total word count - document A 8773
Total word count - document B 0
Total word count - documents A + B 8773

48/3,AB/45 (Item 11 from file: 348)
DIALOG(R)File 348:European Patents

00562000
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RNA and DNA molecules for producing virus resistance.
DNS- und RNS-Molekule zur Erzeugung einer Virus-Resistenz.
Molecules d'ADN et d'ARN pour la production d'une resistance **virale.**
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PATENT (CC, No, Kind, Date): EP 558944 A2 930908 (Basic)
EP 558944 A3 940608
APPLICATION (CC, No, Date): EP 93101710 930204;
PRIORITY (CC, No, Date): DE 4203441 920206
DESIGNATED STATES: BE; CH; DE; DK; FR; GB; IT; LI; NL
INTERNATIONAL PATENT CLASS: C12N-015/11; C12N-001/21; A01H-005/00; A01H-005/10; C12Q-001/68; A01N-063/02; C12N-009/00;

ABSTRACT EP 558944 A2
The invention relates to RNA molecules which are complementary to at least one part of a viral RNA replicative intermediate and which inhibit the viral growth cycle by binding to the RNA replicative intermediate and preferably by specifically cleaving the RNA replicative intermediate, thereby achieving a reliable improvement in virus **resistance** in the desired organisms. (see image in original document)
ABSTRACT WORD COUNT: 62

LANGUAGE (Publication,Procedural,Application): English; English; English
FULLTEXT AVAILABILITY:

Available Text	Language	Update	Word Count
CLAIMS A	(English)	EPABF1	586
SPEC A	(English)	EPABF1	6493
Total word count - document A			7079
Total word count - document B			0
Total word count - documents A + B			7079

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